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(54) Title: CATALYTIC ASYMMETRIC REDUCTION OF TRISUBSTITUTED OLEFINS AND ENAMINES (57) Abstract A catalytic asymmetric reduction process, which, by hydrogenating trisubstituted olefins, yields a corresponding organic compound having a high level of enantiomeric purity is disclosed. The process is also effective for the catalytic asymmetric reduction of certain enamines and related compounds to yield a corresponding amine or related compound, respectively, having a high level of enantiomeric purity. The reduction process utilizes a chiral metal catalyst that includes a metal or metal complex that is selected from groups 3, 4, 5, or 6, lanthanides and actinides. Moreover, the process uses hydrogen as the stoichiometric reducing agent and may be carried out at pressures ranging from about 0.5 to 200 atmospheres. The reaction can also be carried out using an acidic compound as a rate enhancing additive.		

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CATALYTIC ASYMMETRIC REDUCTION OF TRISUBSTITUTED OLEFINS AND ENAMINES

Government Support

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The U.S. Government has rights in this invention pursuant to NIH Grant Number GM 46059.

Background of the Invention

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The present invention relates to processes for the catalytic asymmetric reduction of trisubstituted olefins and for the catalytic asymmetric reduction of certain enamines and related compounds.

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Processes that economically and efficiently produce enantiomerically enriched organic compounds are of great interest since these compounds are widely used as pharmaceuticals and specialty chemicals. More specifically, reactions that reduce trisubstituted olefins to yield enantiomerically enriched products are commercially quite significant as they can be used in the large scale preparation of pharmaceuticals and specialty chemicals. Thus, the effectiveness and economy of such reduction reactions are important considerations.

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Currently utilized methods of producing enantiomerically enriched products by hydrogenation of trisubstituted olefins rely upon the use of expensive late transition metal catalysts such as rhodium and ruthenium. See, Noyori, R. *Science* 1990, 248, 1194-1199; Ojima, I., *et al Tetrahedron* 1989, 45, 6901-39. In addition, many types of trisubstituted olefins cannot be efficiently converted, by hydrogenation, to enantiomerically enriched organic compounds using the catalyst systems currently available.

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Currently, there are no known methods of producing enantiomerically enriched products by hydrogenation of those enamines and related compounds that are 1,1-disubstituted olefins. Such methods would be useful in many synthesis reactions to provide enantiomerically enriched amines and related enantiomerically enriched compounds.

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Accordingly, it would be advantageous to provide more economical and efficient processes for asymmetrically reducing trisubstituted olefins, and to provide an economical and efficient processes for asymmetrically reducing certain enamines and related compounds.

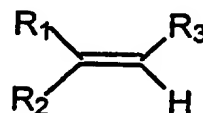
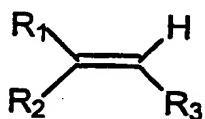
It is thus an object of the invention to provide more economical and effective processes for the asymmetric reduction of trisubstituted olefins. Another object is to provide an effective process to obtain from trisubstituted olefins enantiomerically enriched compounds such as hydrocarbons and functionalized hydrocarbons. It is also an object of the invention to provide economical and effective processes for the asymmetric reduction of enamines that are 1,1-disubstituted olefins. A further object is to provide effective processes to obtain from such enamines enantiomerically enriched amines. Other objects will be apparent upon reading the disclosure that follows.

10 Summary of the Invention

The disclosure of the related parent applications, U.S. patent application serial no. 792,229, filed November 14, 1991 entitled "Catalytic Asymmetric Reduction of Imines and Oximes", U.S. patent application serial no. 698,940, filed May 13, 1991, entitled "Catalytic Asymmetric Reduction of Imines and Oximes", and U.S. patent application serial no. 616,892, filed November 21, 1990, entitled "Catalytic Reduction of Organic Carbonyls", are all hereby incorporated by reference.

Unless otherwise clear from its context, the term "catalyst" is used interchangeably herein to refer both to the metal complexes or precatalysts before their activation as catalytic species, and to the active catalytic species themselves.

The invention provides an effective process for the catalytic asymmetric reduction of trisubstituted olefins to yield chiral organic compounds enriched in one enantiomer. The term trisubstituted olefin refers to a molecule which contains a carbon-carbon double bond with three substituents that are neither hydrogen nor deuterium. Trisubstituted olefins are represented by the general structural formulas shown below.

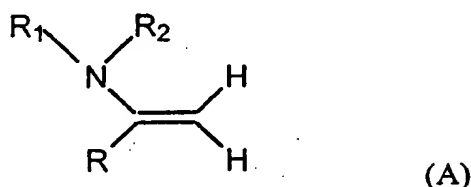


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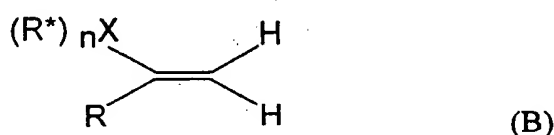
Further the invention provides an effective process for the catalytic asymmetric reduction of those enamines which are 1,1-disubstituted olefins to yield chiral amines enriched in one enantiomer. Hereinafter the term "enamine" is used to refer to those enamines that are 1,1-disubstituted olefins. Such enamines contain a carbon-carbon double bond with one substituent that is an alkyl group (saturated or unsaturated), an aryl group, a heteroaromatic group, or a substituted version thereof. The other substituent on the same

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carbon is either a mono- or di-substituted amino group. Such enamine molecules are represented by the general structural formula:



In addition, other compounds that can be catalytically asymmetrically reduced according to this invention have the general formula



Generally, the process of the invention involves first generating an active species of an effective, optically active reduction catalyst which is used in the reaction. The substrate is then reacted with the active catalyst at a temperature range of 0°C to 100°C and at pressures ranging from 0.5 to 200 atmospheres of hydrogen. When the reaction is complete one need only perform conventional separation and purification techniques to yield the desired enantiomerically enriched end product.

Formation of the active catalyst can be effected by dissolving the precatalyst in an organic solvent in an inert atmosphere or in an atmosphere of hydrogen. Thereafter, the precatalyst/solvent mixture can be subjected to between 1 and 2 equivalents, relative to the amount of precatalyst, of an alkylating or reducing agent. The reaction mixture can then be placed in an atmosphere of hydrogen gas at a pressure between 0.5 and 200 atmospheres. The reaction can then be conducted using hydrogen alone, or in combination with a substoichiometric amount of a silane relative to the amount of substrate.

The process of the invention preferably is carried out where hydrogen serves as the reducing agent. In such an embodiment the active catalytic species is generated under an inert gas such as argon or nitrogen, or under an atmosphere of hydrogen. Thereafter, a substoichiometric quantity of a silane compound (relative to the substrate) may optionally be added. The reduction reaction takes place in an atmosphere of hydrogen which is present in excess and serves as the stoichiometric reductant.

In another embodiment no alkylation is necessary. The reaction is able to proceed by mixing together, in a hydrogen atmosphere, in a suitable reaction vessel, the precatalyst, the desired substrate, and, optionally, a substoichiometric quantity, relative to substrate, of a silane compound.

In another embodiment the reaction is able to proceed by mixing together in a hydrogen or inert atmosphere, in a suitable reaction vessel, the precatalyst, a rate enhancing additive, the desired substrate, and, optionally, a substoichiometric quantity, relative to the substrate, of a silane compound. If carried out under an inert atmosphere hydrogen can be added to the reaction vessel by purging the vessel with hydrogen or by evacuating the inert atmosphere and subsequently adding hydrogen. It is understood that pressure within the vessel can be adjusted to the desired level.

The reduction of both trisubstituted olefins and certain enamines and related compounds by this reaction yields, after quenching of the catalyst, a crude end product in a more reduced form than the starting compound. The end product may then be purified by known techniques.

Detailed Description of the Invention

The process of the invention can be used to effect the catalytic asymmetric reduction of trisubstituted olefins and enamines and related compounds that are 1,1-disubstituted olefins to produce corresponding organic compounds that are enriched in one enantiomer. The catalyst preferably is enriched in one enantiomer. Generally, an enantiomerically enriched catalyst is one which has more than 50 percent of one enantiomer. More specifically, an enantiomerically enriched catalyst is one which has greater than 80%, and most preferably greater than 90% of one enantiomer.

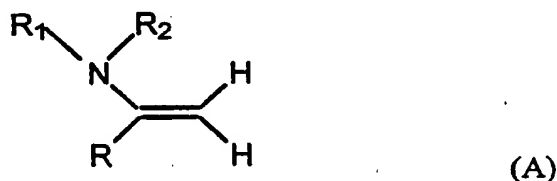
The trisubstituted olefin substrates to which the invention is directed are represented by the formulas shown below.



where R_1 , R_2 and R_3 are neither hydrogen nor deuterium, and where R_1 and R_2 are different. R_1 , R_2 and R_3 can be selected from among a variety of functional groups.

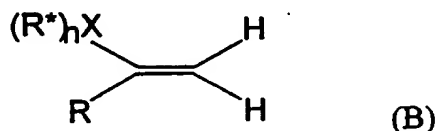
The trisubstituted olefin substrates that are useful with the processes of the present invention are converted to compounds in a more reduced state of having general formula $(H)(R_1)(R_2)CCH_2R_3$, where R_1 is not the same as R_2 and R_1 , R_2 and R_3 are neither H nor D. R_1 and R_2 may be part of a ring system, and R_2 and R_3 may be part of a ring system. Further, R_1 , R_2 and R_3 may be any combination of substituted and/or unsubstituted alkyl, aryl, alkenyl, alkynyl, or heteroaromatic groups, and may be $N(R')R''$, where R' and R'' are aryl and/or alkyl groups, substituted and/or unsubstituted, SR' , where R' is an aryl or alkyl group, substituted or unsubstituted, OR' , where R' is an aryl or alkyl group, substituted or unsubstituted, and $Si(R')(R'')(R''')$, where R' , R'' , R''' are alkyl or aryl groups, substituted or unsubstituted. R_1 , R_2 or R_3 also may be a halogen and/or a COX group, where X is OR' , where R' is an aryl or alkyl group, substituted or unsubstituted, X is $N(R')R''$, where R' and R'' are aryl and/or alkyl groups, substituted or unsubstituted, or X is an alkyl or an aryl group, substituted or unsubstituted.

The enamine and related substrates to which the invention is directed are represented by the formula shown below:



where R is an alkyl group (saturated or unsaturated), an aryl group, a heteroaromatic group, or a substituted version thereof, and where R_1 and R_2 are alkyl groups (saturated or unsaturated), aryl groups, heteroaromatic groups, or substituted versions thereof, or hydrogen, except that R_1 and/or R_2 are not of the formula $C(O)R_3$. Further, R_1 and R_2 may be part of a ring system; or R and R_1 may be part of a ring system; or R and R_2 may be part of a ring system.

Alternatively, the enamine and related substrates of the invention are represented by the formula:



where R is an alkyl group (saturated or unsaturated), an aryl group, a heteroaromatic group or a substituted version thereof, and where R^* may be hydrogen, alkyl, aryl, $Si(R')(R'')(R''')$, a halogen, $-OR'$, $-SR'$, $-NR'(R'')$, $PR'(R'')(R''')$, or $-PR'(R'')$, where R' , R'' and R''' may be H, an

alkyl, aryl, or silyl group and may be different or the same; where X is not H, C, or N; and where n is from 1 to 6.

5 The enamine and related substrates that are useful with the processes of the present invention are converted to amines or related compounds, respectively, in a more reduced state that have the general formula $((R_1)NR_2)(R)(H)CCH_3$, where R is an alkyl group (saturated or unsaturated), an aryl group, a heteraromatic group, or a substituted version thereof, and where R is not H or D. Further, R_1 and R_2 are alkyl groups (saturated or unsaturated), aryl groups, heteraromatic groups, or a substituted version thereof. R_1 and R_2 can also be hydrogen, but R_1 and/or R_2 are not of the formula $C(O)R_3$. R_1 and R_2 further may be part of a ring system; or R_1 and R may be part of a ring system; or R_2 and R may be part of a ring system. Alternatively, the end product has the general formula $[(R^*)_nX](R)C(H)CH_3$, where R is an alkyl group (saturated or unsaturated), an aryl group, a heteroaromatic group, or a substituted version thereof and where R^* is hydrogen, alkyl, aryl, Si(R')(R'')(R'''), a halogen, -OR', -SR', -NR'(R''), PR'(R'')(R'''), or -PR'(R''), where R', R'' and R''' may be H, an alkyl, aryl, or silyl group and may be different or the same.

20 The basic steps of the invention involve first generating an active species of an effective, optically active catalyst. This can be accomplished by dispensing a suitable optically active precatalyst in an organic solvent such as tetrahydrofuran, ether, toluene, benzene, hexane, or the like. Preferably, this mixture is maintained in an atmosphere of an inert gas, such as argon or nitrogen, or in an atmosphere of hydrogen gas. In some instances, especially where certain titanium-containing catalysts are used, as explained below in more detail, the precatalyst may be activated by dissolving the catalyst in a solvent, followed by the addition of an alkylating agent. Thereafter, a substoichiometric quantity of a silane compound, relative to the substrate, may optionally be added to the reaction mixture. The desired substrate is added to the mixture and the reactants may be transferred to a reaction vessel that is able to be charged with hydrogen at ambient or elevated pressures.

30 The reduction reactions of the present invention preferably use hydrogen as the stoichiometric reducing agent. The hydrogen reducing agent can be used alone, or it can be used in combination with a substoichiometric amount, relative to the substrate, of a silane compound.

35 Where the reaction is to be conducted using hydrogen as the reducing agent at high pressure, the precatalyst/solvent mixture is, optionally, subjected to vacuum to remove the inert gas, and hydrogen gas can then be added to the reactor vessel. The reactor vessel contents can then be cooled to about 0°C and allowed to equilibrate. Thereafter, an alkylating agent is generally added to the reactor vessel. Optionally, a silane compound can

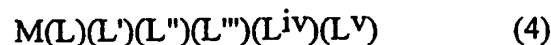
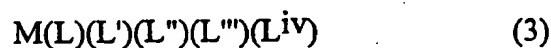
then be added at a substoichiometric amount relative to the substrate. The desired substrate is then added and the reaction vessel can be sealed and placed in a dry box. The vessel is then transferred to a high pressure reactor (such as a Parr[®] high pressure reactor) and it is removed from the dry box. The reactor is then charged with hydrogen at a desired pressure and the reaction commences upon heating to between 25 - 100° C. The reaction can be conducted in hydrogen at a pressure ranging from 0.5 atmosphere to over 200 atmospheres.

The reaction typically requires from 1 to 200 hours to complete. Once completed, the reaction vessel is cooled to room temperature, vented and opened to air to quench the catalyst. Well known separation and purification techniques can then be utilized to obtain the end product, which is enriched in one enantiomer.

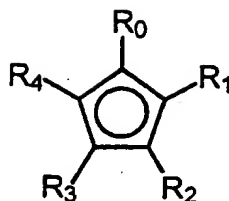
One of ordinary skill in the art will appreciate that minor modifications may be made to the reduction reaction without exceeding the scope of the invention. To some extent the Examples presented herein illustrate alternative techniques for conducting reduction reactions according to the invention.

The present reduction reaction preferably requires between about 0.1 - 40% by mole of catalyst relative to the substrate, and more preferably, between about 5 - 10% by mole of catalyst relative to the substrate.

A variety of precatalysts can be used effectively in the reduction reactions of the present invention. Exemplary precatalysts broadly include those that are chiral, either by virtue of the chirality of a ligand or by virtue of chirality at the metal center. Exemplary precatalysts are chiral precatalysts having the general formulas:



where M is a group 3, 4, 5 or 6 metal, a lanthanide, or an actinide and where L, L', L'', and L''', L^{iv} and L^v, independently, can be some combination of H, an alkyl group, an aryl group, a cyclopentadienyl group, Si(R)(R')(R''), a halogen, -OR, -SR, -NR(R'), or PR(R')(R''), where R, R' and R'' may be H, an alkyl, aryl, or silyl group and may be different or the same. A cyclopentadienyl group (designated "Cp") is represented by the formula



where R_0 , R_1 , R_2 , R_3 , and R_4 may be hydrogen, alkyl, aryl, $\text{Si}(\text{R})(\text{R}')(\text{R}'')$, a halogen, $-\text{OR}$, $-\text{SR}$, $-\text{NR}(\text{R}')$, $\text{PR}(\text{R}')(\text{R}'')$, or $-\text{PR}(\text{R}')$, where R , R' and R'' may be H, an alkyl, aryl, or silyl group and may be different or the same. Examples of group 3, 4, 5 or 6 metals which may be useful with the present invention include titanium, vanadium, niobium, and chromium. Examples of useful lanthanides include yttrium, scandium, lanthanum, samarium, ytterbium, and lutetium. Examples of useful actinides include thorium and uranium. Titanium, however, is the most preferred metal.

A preferred precatalyst, which is particularly useful in conducting catalytic asymmetric reduction reactions is generally represented by the formula



where Y represents a substituted cyclopentadienyl or indenyl group or where Y_2 represents a substituted bis-cyclopentadienyl or bis-indenyl group; M represents a group 3, 4, 5, 6 metal, a lanthanide or an actinide; X represents groups including halides, alkoxides, amides, sulfides, phosphines, alkyls, aryls, hydrides, and mono-, di-, and tri-substituted silyls, and carbon monoxide; and X_2 can be an η^2 -olefin or an η^2 -alkyne; and n is an integer from 1 to 4. In a preferred embodiment Y_2 is ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl) and X_2 represents 1,1'-binaphth-2,2'-diolate.

Precatalysts having the ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl) backbone are referred to herein as "BIE" catalysts. Specific preferred catalysts for asymmetric reduction include (R,R)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium-(R)-1,1'-binaphth-2,2'-diolate; (S,S)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium-(S)-1,1'-binaphth-2,2'-diolate; (R,R)-1,1'-Trimethylenebis(η^5 -3-tertbutylcyclopentadienyl)-titanium(IV) dichloride; (S,S)-1,1'-Trimethylenebis(η^5 -3-tertbutylcyclopentadienyl)-titanium(IV) dichloride; (R,R)-Ethylene-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium(IV) dichloride; (S,S)-Ethylene-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium(IV) dichloride; (R,R)-2,2'-Bis(1-indenylmethyl)1-1'-binaphthyl titanium(IV) dichloride; (S,S)-2,2'-Bis(1-indenylmethyl)1-1'-binaphthyl titanium(IV)

dichloride; (R,R)-Ethylene-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl) dimethyl titanium(IV); and (S,S)-Ethylene-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl) dimethyl titanium(IV).

5 The BIE-type precatalysts useful with the catalytic asymmetric reduction reactions of the invention are enriched in one enantiomer of the molecule. Enantiomeric enrichment, as the term is used herein, requires more than 50% of one enantiomer, and more preferably requires more than 80% of one enantiomer. In a preferred embodiment, an enantiomerically enriched catalyst has more than 90% of one enantiomer.

10 Other preferred catalysts include metal alkoxides and metal aryloxides such as titanium alkoxides and titanium (IV) aryloxides. Specific examples of such catalysts include (R,R)-2,2'-Dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis(β -naphthyl)-1,3-dioxolan-4,5-dimethoxy diisopropoxy titanium(IV) and (S,S)-2,2'-Dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis(β -naphthyl)-1,3-dioxolan-4,5-dimethoxy diisopropoxy titanium(IV).

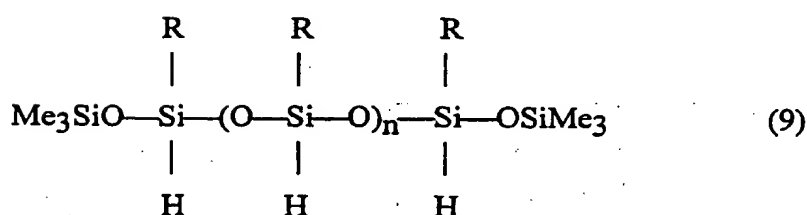
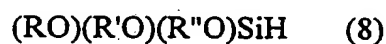
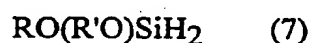
15 Precatalysts, including BIE catalysts, may need to be activated by reaction with an alkylating agent or reducing agent, preferably in an organic solvent. Suitable alkylating agents are known to those skilled in the art and generally include organometallic compounds. Examples of such compounds include alkylmagnesium halides, alkyllithium
20 compounds, alkyl aluminum compounds and boron, aluminum, or other metal alkyls or metal hydrides. Particularly preferred alkylating agents include n-pentylmagnesium bromide and n-butyllithium. Preferred reducing agents include sodium bis(2-methoxyethoxy) aluminum hydride (Red Al[®]). Preferably, about 100 to 200% by mole of the alkylating agent (relative to precatalyst) should be reacted with the precatalyst in order for activation to occur. The
25 activation of such catalysts by reaction with an alkylating agent is further described and illustrated in the examples.

30 Metal alkoxide and metal aryloxide catalysts may be air stable, and may be self-activating (i.e., require no alkylation step), or may be activated by the presence of a silane compound.

The catalysts useful in this invention may be active as electronically neutral molecules, anions or cations.

35 One skilled in the art will appreciate that a variety of solvents may be used with these catalysts. One general requirement of a suitable solvent is that the catalyst must be completely or partially soluble within the solvent. Complete solubility is not required as there need only be enough catalyst present in the solution to facilitate a reaction. Exemplary solvents include tetrahydrofuran, toluene, benzene, hexane, ether and the like.

As noted above, hydrogen is the reducing reagent used in the present catalytic asymmetric reduction processes. Hydrogen may be used alone or in the presence of a substoichiometric amount (relative to the substrate) of a silane compound. A suitable silane compound is one that possesses a silicon-hydrogen bond. Exemplary silane compounds which may be used in these processes (with a hydrogen reducing agent) are represented by the formulas shown below.



where R, R' and R'' represent alkyl, aryl or hydride groups and may be the same or different. Specific examples of suitable silane reducing reagents include silane, diphenylsilane, phenylsilane, diethylsilane, dimethylsilane, triethoxysilane, trimethoxysilane, and poly(methylhydrosiloxane).

The silane compound, when used in a substoichiometric amount, can be present at about 0.1 to 5 equivalents, and more preferably 0.1-2.5 equivalents, relative to the catalyst.

The rate enhancing additive is an acidic compound. Preferably this additive is tris(perfluorophenyl) boron or an ammonium salt of perfluorotetraphenylborate having the formula $[\text{HNR}_3]^+ [\text{B}(\text{C}_6\text{F}_5)_4]^-$. The rate enhancing additive can be used at 0.01 to 100 equivalents relative to the catalyst. Preferably this additive is used at or less than 1 equivalent relative to the catalyst.

One aspect of the invention, as noted above, involves the catalytic asymmetric reduction of trisubstituted olefins to yield organic compounds having a high degree of

enantiomeric purity. The desired trisubstituted olefin substrate can be reduced to yield a product enriched in one enantiomer, using a suitable catalyst of the type described above, which is enriched in one enantiomer. A preferred catalyst is one which is enriched in (R,R)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium-(R)-1,1'-binaphth-2,2'-diolate.

- 5 Another preferred catalyst is one which is enriched in (S,S)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium-(S)-1,1'-binaphth-2,2'-diolate. Preferably, these catalysts contain at least about 80% of the (R, R, R) or (S,S,S) enantiomers, respectively.

- 10 The degree of enantiomeric excess ("ee") for the reaction product depends on a number of factors including the enantiomeric purity of the catalyst, the specific trisubstituted olefin substrate being reduced, and the reaction conditions. Many reactions conducted according to the process of the present invention yield end products having relatively high enantiomeric excesses. In some instances, the ee exceeds 90%.

- 15 The asymmetric reduction of trisubstituted olefin and certain enamine substrates is further described and illustrated by the examples that follow.

EXAMPLES

- 20 In examples 1 through 9 that follow all reactions were conducted under an atmosphere of argon, nitrogen or hydrogen using standard Schlenk and glove box techniques. Hydrogenation reactions were conducted in a glass pressure reaction vessel (purchased from Aerosol Lab Equipment, Walton, NY 13856) or in a Parr® Model 4751 high pressure reaction vessel. The enantiomeric excess values of the products were determined by HPLC
25 analysis using a Chiralcel OD column, unless otherwise noted. HPLC chromatograms were compared with those of the racemic alkanes.

EXAMPLE 1: *Reduction of E-3-(4-methoxyphenyl)-2-methyl-1-methoxy-2-propene to 3-(4-methoxyphenyl)-2-methyl-1-methoxypropane*

- 30 In a dry sealable Schlenk flask under an argon atmosphere 0.0573 g (0.096 mmol) of (S,S)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (S)-1,1'-binaphth-2,2'-diolate was dissolved in THF (10 mL). The vessel was degassed by exposure to vacuum (2 x 10 sec) and put under an atmosphere of hydrogen and subsequently cooled to 0°C in an
35 ice water bath. After equilibration, a solution of n-butyllithium (0.123 mL, 1.52 M in hexanes, 0.187 mmol, 1.95 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.030 mL, 0.236 mmol, 2.4 equiv) was then added followed, after 5 minutes, by E-3-(4-methoxyphenyl)-2-methyl-1-methoxy-2-propene (0.345g, 1.92 mmol, 20 equiv). The flask was sealed and the solution moved into a dry box and transferred to a Parr® high

pressure reaction vessel containing a magnetic stir bar. The vessel was sealed and moved to a fume hood where it was charged to ~2000 psig with hydrogen and placed in an oil bath at 65°C. The reaction mixture was allowed to stir for 43.5 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/hexane (1/4) and water and separating the layers. The aqueous layer was extracted twice with ether / hexane and the combined organic layers were dried over MgSO₄. The solvent was removed *in vacuo* and the residue distilled at reduced pressure to yield 0.225g (1.42 mmol, 74%) of 3-(4-methoxyphenyl)-2-methyl-1-methoxypropane which had an ee of 92.7%.

EXAMPLE 2: Reduction of *E*-1,2-diphenylpropene to *R*(-)-1,2-Diphenylpropane

In a dry sealable Schlenk flask under an argon atmosphere 0.102 g (0.171 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (16 mL). The vessel was degassed by exposure to vacuum (2 x ~10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of *n*-butyllithium (0.211 mL, 1.58 M in hexanes, 0.333 mmol, 1.95 equiv) was added and the mixture was allowed to stir for 10 min at which point it was a green color. Phenylsilane (0.055 mL, 0.432 mmol 2.4 equiv) was then added. The flask was sealed and the solution moved into a dry box and transferred to a Parr® high pressure reaction vessel containing a magnetic stir bar and *E*-1,2-diphenylpropene (0.66g, 3.36 mmol, 20 equiv). The pressure vessel was sealed and moved to a fume hood where it was charged to 1500 psig with hydrogen and placed in an oil bath at 65°C. The reaction mixture was allowed to stir for 65 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/hexane (1/4) and water and separating the layers. The organic extract was concentrated and was run through a 50 mL plug of silica gel to yield 0.628g (3.2 mmol, 94%) of *R*(-)-1,2-Diphenylpropane. The ee was found, polarimetrically, to be greater than 99%.

EXAMPLE 3: Reduction of 6-methoxy-1-methyl-3,4-dihydronaphthalene to 6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene

In a dry sealable Schlenk flask under an argon atmosphere 0.0592 g (0.099 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (10 mL). The vessel was degassed by exposure to vacuum (2 x ~10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of *n*-butyllithium (0.122 mL, 1.58 M in hexanes, 0.193 mmol, 1.95 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.031 mL, 0.243 mmol, 2.5 equiv) and 0.378g (2.19 mmol, 22 equiv) 6-

methoxy-1-methyl-3,4-dihydronaphthalene were then added. The flask was sealed and the solution moved into a dry box and transferred to a Parr[®] high pressure reaction vessel containing a magnetic stir bar. The pressure vessel was sealed and moved to a fume hood where it was charged to 1800 psig with hydrogen and placed in an oil bath at 68°C. The reaction mixture was allowed to stir for 132 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether hexane (1/4) and water and separating the layers. The organic extract was concentrated and chromatographed on 50 mL silica gel to yield 0.268g (1.54 mmol, 70%) of 6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene with an ee of 94.7%.

EXAMPLE 4: *Reduction of 1-methyl-3,4-dihydronaphthalene to 1-methyl-1,2,3,4-tetrahydronaphthalene*

In a dry sealable Schlenk flask under an argon atmosphere 0.059g (0.099 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (10 mL). The vessel was degassed by exposure to vacuum (2 x ~10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of n-butyllithium (0.125 mL, 1.58 M in hexanes, 0.196 mmol, 1.96 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.033 mL, 0.259 mmol, 2.6 equiv) and 0.273 g (1.87 mmol, 19 equiv) 1-methyl-3,4-dihydronaphthalene were then added. The flask was sealed and the solution moved into a dry box and transferred to a Parr[®] high pressure reaction vessel containing a magnetic stir bar. The pressure vessel was sealed and moved to a fume hood where it was charged to 2150 psig with hydrogen and placed in an oil bath at 65°C. The reaction mixture was allowed to stir for 184 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/ hexane (1/4) and water and separating the layers. The organic extract was distilled at reduced pressure to yield 0.195 g (1.31 mmol, 70%) of 1-methyl-1,2,3,4-tetrahydronaphthalene with an ee of 70 %, determined polarimetrically.

EXAMPLE 5: *Reduction of E-2-(4-methoxyphenyl)-2-butene to 2-(4-methoxyphenyl)butane*

In a dry sealable Schlenk flask under an argon atmosphere 0.0364 g (0.061 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (10 mL). The vessel was degassed by exposure to vacuum (2 x ~10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of n-butyllithium (0.075 mL, 1.58 M in hexanes, 0.118 mmol, 1.94 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.017 mL, 0.133 mmol, 2.4 equiv) and 0.189 g (1.17 mmol, 19.2 equiv) *E*-2-(4-

methoxyphenyl)-2-butene were then added. The flask was sealed and the solution moved into a dry box and transferred to a Parr® high pressure reaction vessel containing a magnetic stir bar. The pressure vessel was sealed and moved to a fume hood where it was charged to 2100 psig with hydrogen and placed in an oil bath at 69°C. The reaction mixture was allowed to stir for 65 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/ hexane (1/4) and water and separating the layers. The organic extract was distilled at reduced pressure to yield 0.133g (0.811 mmol, 69%) of 2-(4-methoxyphenyl)propane with an ee of 96.2%.

10 **EXAMPLE 6:** *Reduction of 7-methoxy-2-methyl-3,4-dihydronaphthalene to 7-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalene*

In a dry sealable Schlenk flask under an argon atmosphere 0.0254 g (0.043 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (5 mL). The vessel was degassed by exposure to vacuum (2 x ~10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of n-butyllithium (0.052 mL, 1.58 M in hexanes, 0.083 mmol, 1.91 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.016 mL, 0.126 mmol, 2.9 equiv) and 0.130 g (0.756 mmol, 18 equiv) 7-methoxy-2-methyl-3,4-dihydronaphthalene were then added. The flask was sealed and the solution moved into a dry box and transferred to a Parr® high pressure reaction vessel containing a magnetic stir bar. The pressure vessel was sealed and moved to a fume hood where it was charged to 2150 psig with hydrogen and placed in an oil bath at 70°C. The reaction mixture was allowed to stir for 44 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/ hexane (1/4) and water and separating the layers. The organic extract was distilled at reduced pressure to yield 0.097 g (0.557 mmol, 73%) of 7-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalene with an ee of 90.4%.

30 **EXAMPLE 7:** *Reduction of E-N,N-Dibenzyl-3-phenyl-2-buten-1-amine to N,N-Dibenzyl-3-phenylbutyl-1-amine*

In a dry sealable Schlenk flask under an argon atmosphere 0.0551 g (0.0922 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7 - tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (10 mL). The vessel was degassed by exposure to vacuum (2 x ~10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of n-butyllithium (0.118 mL, 1.52 M in hexanes, 0.179 mmol, 1.95 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.029 mL, 0.126 mmol, 2.5 equiv) and 0.550 g (1.68 mmol, 18 equiv) *E*-N,N-

Dibenzyl-3-phenyl-2-buten-1-amine were then added. The flask was sealed and the solution moved into a dry box and transferred to a Parr[®] high pressure reaction vessel containing a magnetic stir bar. The pressure vessel was sealed and moved to a fume hood where it was charged to 2000 psig with hydrogen and placed in an oil bath at 65°C. The reaction mixture was allowed to stir for 43 h. The vessel was cooled to room temperature, vented and opened to air. The extraction mixture was treated with 3 N HCl (aq); the solid salt isolated from this treatment was neutralized with 15% NaOH and subsequently partitioned between CH₂Cl₂ and water. The organic extract was concentrated to yield 0.43 g (1.30 mmol, 74%) of N,N-Dibenzyl-3-phenylbutyl-1-amine which had an ee of 95.3%.

Example 8: *Reduction of E-N,N-Dibenzyl-3-phenyl-2-buten-1-amine to N,N-Dibenzyl-3-phenylbutylamine with EBTHITiCl₂*

In a dry sealable Schlenk flask under an argon atmosphere 0.0363 g (0.0948 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium dichloride was dissolved in THF (10 mL). The vessel was degassed by exposure to vacuum (2x ~ 10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of n-butyllithium (0.15 mL, 1.22 M in hexanes, 0.183 mmol, 1.93 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.035 mL, 0.275 mmol, 2.9 equiv) was added, the flask was sealed and the solution moved into a dry box. It was added to a Parr[®] high pressure reaction vessel containing a magnetic stir bar and 0.182g (0.57 mmol, 6 equiv) *E*-N,N-dibenzyl-3-phenyl-2-buten-1-amine. The pressure vessel was sealed and moved to a fume hood where it was charged to 1950 psig with hydrogen and placed in an oil bath at 65°C. The reaction mixture was allowed to stir for 54 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/hexane (1:4) and water. The organic extract was concentrated and was chromatographed on 20 mL silica gel with a 1/6 to 1/3 gradient of CH₂Cl₂/hexane to yield 0.133g (0.416 mmol, 73%) of N,N-dibenzyl-3-phenyl-butyl-1-amine, which had an ee of 94.4%.

EXAMPLE 9: *Reduction of E-1,2-diphenylpropene to R(-)-1,2-Diphenylpropane*

In a dry sealable Schlenk flask under an argon atmosphere 0.0599g (0.100 mmol) (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate was dissolved in THF (10mL). The vessel was degassed by exposure to vacuum (2x ~ 10 sec), put under an atmosphere of hydrogen and subsequently cooled to 0°C in an ice water bath. After equilibration, a solution of n-butyllithium (0.128 mL, 1.52 M in hexanes, 0.194 mmol, 1.94 equiv) was added and the mixture was allowed to stir for 10 min. Phenylsilane (0.032 mL, 0.25 mmol 2.5 equiv) was then added. The contents were then

cannula transferred to a pressure vessel containing a magnetic stir bar and *E*-1,2-diphenylpropene (0.138g, 1.96 mmol, 20 equiv) under an atmosphere of hydrogen. The pressure vessel was sealed and moved to a fume hood where it was charged to 89 psig with hydrogen and placed in an oil bath at 65°C. The reaction mixture was allowed to stir for 19 h. The vessel was cooled to room temperature, vented and opened to air. The reaction mixture was worked up by partitioning between diethyl ether/hexane (1/4) and water and separating the layers. The organic extract was concentrated and was run through a 50 mL plug of silica gel to yield 0.304g (1.55 mmol, 80%) of *R*(-)-1,2-Diphenylpropane, with an ee of >99% as determined polarimetrically.

In examples 10 through 14 that follow all reactions were conducted under an atmosphere of argon or hydrogen using standard Schlenk techniques. Hydrogenation reactions were conducted in a Schlenk flask or in a Fisher-Porter bottle (purchased from Aerosol Lab Equipment, Walton, NY 13856). The enantiomeric excess values of the products were determined by analysis of ¹H NMR spectra of diastereomeric salts resulting from addition of (*R*) or (*S*) acetyl mandelic acid to the amines.

EXAMPLE 10: *Reduction of 1-(1-pyrrolidinyl)-1-phenylethene to (R)-1-(1-pyrrolidinyl)-1-phenylethane.*

In a dry sealable Schlenk flask (300 mL) under a hydrogen atmosphere, (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate (35 mg, 0.058 mmol) was dissolved in THF (4 mL). A solution of *n*-butyllithium (0.065 mL, 1.7M in hexanes, 0.11 mmol, 1.91 equiv.) was added at which point the reaction turned from a dark red color to a green color. Phenylsilane (0.02 mL, 0.162 mmol, 2.7 equiv.) was added followed by a solution of 1-(1-pyrrolidinyl)-1-phenylethene (200 mg, 1.16 mmol, 20 equiv.) in THF (1 mL). The flask was sealed and the reaction mixture was stirred for 20 h at room temperature. The reaction was opened to air and the solvent was removed using a rotary evaporator. The crude residue was purified by chromatography on silica gel using methanol in methylene chloride (2.5% methanol in methylene chloride increased to 10%) to give, after concentration *in vacuo*, (*R*)-1-(1-pyrrolidinyl)-1-phenylethane (159 mg, 0.91 mmol, 78%). The amine had an ee of 94%.

EXAMPLE 11: *Reduction of 1-(1-pyrrolidinyl)-1-phenylethene to (S)-1-(1-pyrrolidinyl)-1-phenylethane.*

In a dry sealable Schlenk flask (300 mL) under a hydrogen atmosphere, (*R,R*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*R*)-1,1'-binaphth-2,2'-diolate (35 mg, 0.058 mmol) was dissolved in THF (4 mL). A solution of *n*-butyllithium (0.065 mL,

1.7M in hexanes, 0.11 mmol, 1.91 equiv.) was added at which point the reaction turned from a dark red color to a green color. Phenylsilane (0.02 mL, 0.162 mmol, 2.7 equiv.) was added followed by a solution of 1-(1-pyrrolidinyl)-1-phenylethene (200 mg, 1.25 mmol, 21 equiv.) in THF (1 mL). The flask was sealed and the reaction mixture was stirred for 44 h at room temperature. The reaction was opened to air and the solvent was removed using a rotary evaporator. The crude residue was purified by chromatography on silica gel using methanol in methylene chloride (2.5% methanol in methylene chloride increased to 10%) to give, after concentration *in vacuo*, (S)-1-(1-pyrrolidinyl)-1-phenylethane (125 mg, 0.71 mmol, 57%). The amine had an ee of 94%.

EXAMPLE 12: *Reduction of 1-(1-pyrrolidinyl)-1-(2'-naphthyl) ethene to 1-(1-pyrrolidinyl)-1-(2'-naphthyl) ethane.*

In a dry sealable Schlenk flask (300 mL) under a hydrogen atmosphere, (S,S)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (S)-1,1'-binaphth-2,2'-diolate (35 mg, 0.058 mmol) was dissolved in THF (4 mL). A solution of n-butyllithium (0.065 mL, 1.7M in hexanes, 0.11 mmol, 1.91 equiv.) was added at which point the reaction turned from a dark red color to a green color. Phenylsilane (0.02 mL, 0.162 mmol, 2.7 equiv.) was added followed by a solution of 1-(1-pyrrolidinyl)-1-(2'-naphthyl) ethene (200 mg, 0.98 mmol, 17 equiv.) in THF (1 mL). The flask was sealed and the reaction mixture was stirred for 24 h at room temperature. The reaction was opened to air and the solvent was removed using a rotary evaporator. The crude residue was purified by chromatography on silica gel using methanol in methylene chloride (2.5% methanol in methylene chloride increased to 10%) to give, after concentration *in vacuo*, 1-(1-pyrrolidinyl)-1-(2'-naphthyl) ethane (172 mg, 0.76 mmol, 78%). The amine had an ee of 95%.

EXAMPLE 13: *Reduction of 1-(1-pyrrolidinyl)-1-(2'-methylphenyl) ethene to 1-(1-pyrrolidinyl)-1-(2-methylphenyl) ethane.*

A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and pressure release valve was charged with (S,S)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (S)-1,1'-binaphth-2,2'-diolate (35 mg, 0.058 mmol). The system was evacuated and filled with hydrogen (5-10 psig). THF (4 mL) was added and the hydrogen pressure was increased to 80 psig. With a needle the bottle was vented until the hydrogen pressure was reduced back to 5-10 psig. A solution of n-butyllithium (0.065 mL, 1.7M in hexanes, 0.11 mmol, 1.91 equiv.) was added at which point the reaction turned from a dark red color to a green color. Phenylsilane (0.02 mL, 0.162 mmol, 2.7 equiv.) was added and the hydrogen pressure was increased to 80 psig. Using a high pressure syringe, a solution of 1-(1-pyrrolidinyl)-1-(2-methylphenyl) ethene

(200 mg, 1.18 mmol, 20 equiv.) in THF (1 mL) was added. The reaction mixture was sealed and placed in an oil bath at 65°C for 24 h. The reaction was cooled to room temperature and opened to air. The solvent was removed using a rotary evaporator and the crude residue was purified by chromatography on silica gel using methanol in methylene chloride (2.5% methanol in methylene chloride increased to 10%) to give, after concentration *in vacuo*, 1-(1-pyrrolidinyl)-1-(2-methylphenyl) ethane (189 mg, 1.01 mmol, 86%). The amine had an ee of 96%.

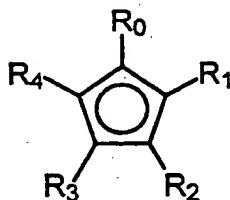
EXAMPLE 14: *Reduction of 1-(4-morpholinyl)-1-(4-methoxyphenyl) ethene to 1-(4-morpholinyl)-1-(4-methoxyphenyl) ethane.*

A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and pressure release valve was charged with (*S,S*)-ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl)titanium (*S*)-1,1'-binaphth-2,2'-diolate (35 mg, 0.058 mmol). The system was evacuated and filled with hydrogen (5-10 psig). THF (4 mL) was added and the hydrogen pressure was increased to 80 psig. With a needle the bottle was vented until the hydrogen pressure was reduced back to 5-10 psig. A solution of n-butyllithium (0.065 mL, 1.7M in hexanes, 0.11 mmol, 1.91 equiv.) was added at which point the reaction turned from a dark red color to a green color. Phenylsilane (0.02 mL, 0.162 mmol, 2.7 equiv.) was added and the hydrogen pressure was increased to 80 psig. Using a high pressure syringe, a solution of 1-(4-morpholinyl)-1-(4-methoxyphenyl) ethene (220 mg, 1.00 mmol, 17 equiv.) in THF (1 mL) was added. The reaction mixture was sealed and placed in an oil bath at 65°C for 23 h. The reaction was cooled to room temperature and opened to air. The solvent was removed using a rotary evaporator and the crude residue was purified by chromatography on silica gel using methanol in methylene chloride (2.5% methanol in methylene chloride increased to 10%) to give, after concentration *in vacuo*, 1-(4-morpholinyl)-1-(4-methoxyphenyl) ethane (185 mg, 0.84 mmol, 84%). The amine had an ee of 91%.

The above examples are intended to be illustrative of the invention and should not be read to limit the invention to the specific reduction reactions provided in the examples. One skilled in the art will readily appreciate that the invention is applicable to a variety of reduction reactions in which the substrate is a trisubstituted olefin, and that a variety of catalysts may be used in these reduction reactions.

CLAIMS:

1. A catalytic asymmetric reduction process, comprising the steps of:
 providing a catalytic amount of an active species of an
 enantiomerically enriched chiral catalyst selected from the group consisting of $M(L)(L')(L'')$,
 $M(L)(L')(L'')(L''')$, $M(L)(L')(L'')(L''')(L^{IV})$, and $M(L)(L')(L'')(L''')(L^{IV})(L^V)$, where M is a
 5 group 3, 4, 5 or 6 metal, a lanthanide or an actinide, and L, L', L'', L''', L^{IV}, L^V,
 independently, is some combination of H, alkyl, aryl, Si(R)(R')(R''), halogen, -OR, -SR, or
 -NR(R'), PR(R')(R''), or a cyclopentadienyl group having the formula



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where R, R', and R'' are H, alkyl, aryl, or silyl and may be different or the same, and where
 R_0 , R_1 , R_2 , R_3 , and R_4 are hydrogen, alkyl, aryl, Si(R)(R')(R''), halogen, -OR, -SR, -NR(R'),
 PR(R')(R''), or -PR(R') groups in any combination, where R, R', and R'' are as defined above;

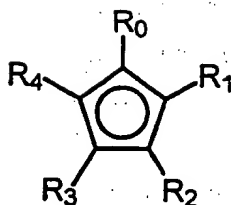
- 15 reacting a substrate selected from the group consisting of trisubstituted olefins
 and enamines in the presence of hydrogen and the catalyst; and
 recovering and purifying a reduced organic reaction product having a high
 level of enantiomeric purity.

2. The process of claim 1 wherein the step of reacting the substrate in the
 20 presence of a hydrogen reducing agent and the catalyst is conducted at a hydrogen pressure in
 the range of 0.5 atmosphere to 200 atmospheres.

3. The process of claim 2 wherein before the step of reacting the substrate
 in the presence of hydrogen and the catalyst, a silane compound is added at a
 25 substoichiometric amount relative to the substrate.

4. The process of claim 1 wherein the enantiomerically enriched chiral
 catalyst is a titanium-containing catalyst selected from the group consisting of
 $L(L')(L'')Ti$; $L(L')(L'')(L''')Ti$; $L(L')Ti-X$; $L(L')(L'')Ti-X$; $L(L')Ti-X_2$; $L(L')Ti-H$; and
 30 $L(L')(L'')TiH$ where X is a halogen, and where L, L', L'' and L''', independently, is some
 combination of H, alkyl, aryl, Si(R)(R')(R''), halogen, -OR, -SR, or -NR(R'), PR(R')(R''), or a
 cyclopentadienyl group of the structure

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where R, R', and R'' are H, alkyl, aryl, or silyl and may be different or the same, and where R₀, R₁, R₂, R₃, and R₄ are hydrogen, alkyl, aryl, Si(R)(R')(R''), halogen, -OR, -SR, -NR(R'), PR(R')(R''), or -PR(R') groups in any combination, where R, R', and R'' are as defined above.

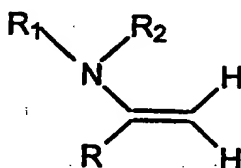
5. The process of claim 4 wherein the catalyst is an enantiomerically enriched chiral complex selected from the group consisting of chiral bis(cyclopentadienyl) titanium monohalide complexes; chiral bis(cyclopentadienyl) titanium monoalkoxide complexes; chiral bis(cyclopentadienyl) titanium dihalide complexes; chiral bis(cyclopentadienyl) titanium dialkoxide complexes; and chiral bis(cyclopentadienyl) titanium diaryloxide complexes.

6. The process of claim 5 wherein the catalyst is selected from the group consisting of (R,R)-ethylene-1,2-bis(η^5 -4, 5, 6, 7-tetrahydro-1-indenyl) titanium-(R)-1,1-binaphth-2,2'-diolate and (S,S)-ethylene-1,2-bis(η^5 -4, 5, 6, 7-tetrahydro-1-indenyl) titanium-(S)-1,1-binaphth-2,2'-diolate.

7. The process of claim 1 wherein the catalyst is present at about 0.1 to 10% by mole, relative to the substrate.

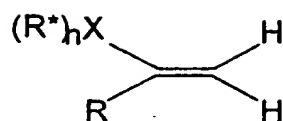
8. The process of claim 7 wherein the reaction is conducted at a temperature ranging from about 0 to 100°C.

9. The process of claim 1 wherein the enamine substrate is represented by the formulas



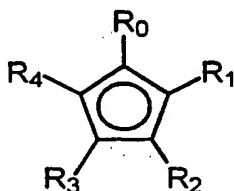
where R is an alkyl group (saturated or unsaturated), an aryl group, a heteraromatic group, or a substituted version thereof, and R₁ and R₂ are hydrogen, alkyl groups (saturated or unsaturated), aryl groups, heteraromatic groups, or a substituted version thereof, except that R₁ and/or R₂ are not of the formula C(O)R₃, or

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where R is an alkyl group (saturated or unsaturated), an aryl group, a heteroaromatic group, or a substituted version thereof and where R* is hydrogen, alkyl, aryl, Si(R')(R'')(R'''), a halogen, -OR', -SR', -NR'(R''), PR'(R'')(R'''), or -PR'(R''), where R', R'' and R''' may be H, an alkyl, aryl, or silyl group and may be different or the same, where X is not H, C, or N, and where n is from 1 to 6.

10. A catalytic asymmetric reduction process, comprising the steps of:
 providing a catalytic amount of an active species of an enantiomerically enriched chiral catalyst selected from the group consisting of M(L)(L')(L''), M(L)(L')(L'')(L'''), M(L)(L')(L'')(L''')(L^{iv}), and M(L)(L')(L'')(L''')(L^{iv})(L^v), where M is a group 3, 4, 5 or 6 metal, a lanthanide or an actinide, and L, L', L'', L''', L^{iv}, L^v, independently, is some combination of H, alkyl, aryl, Si(R)(R')(R''), halogen, -OR, -SR, or -NR(R'), PR(R')(R''), or a cyclopentadienyl group having the formula



- where R, R', and R'' are H, alkyl, aryl, or silyl and may be different or the same, and where R₀, R₁, R₂, R₃, and R₄ are hydrogen, alkyl, aryl, Si(R)(R')(R''), halogen, -OR, -SR, -NR(R'), PR(R')(R''), or -PR(R') groups in any combination, where R, R', and R'' are as defined above;
 providing a rate enhancing additive selected from an acidic compound, present in an amount from 0.01 to 100 equivalents relative to the catalyst;
 reacting a substrate selected from the group consisting of trisubstituted olefins and enamines in the presence of hydrogen and the catalyst; and
 recovering and purifying a reduced organic reaction product having a high level of enantiomeric purity.

11. The process of claim 10 wherein the acidic compound is selected from the group consisting of tris(perfluorotetraphenyl) boron and an ammonium salt of perfluorotetraphenyl borate.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 94/07609

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07B53/00 C07B43/04 C07B35/02 //C07C5/03,C07C209/70,
C07D295/02,C07C41/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07B C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 09545 (MIT) 11 June 1992 see claims 43,53-55; examples 10-12 ---	1-11
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.109, no.26, 23 December 1987, WASHINGTON, DC US pages 8105 - 8107 R. L. HALTERMAN ET AL 'A Designed Enantiomerically Pure, Fused Cyclopentadienyl Ligand with C2 Symmetry: Synthesis and Use in Enantioselective Titanocene-Catalyzed Hydrogenations of Alkenes' see the whole document --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

20 September 1994

Date of mailing of the international search report

13. 10. 94

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TETRAHEDRON LETTERS., vol.27, no.46, 1986, OXFORD GB pages 5599 - 5602 L. A. PAQUETTE ET AL 'Transition Metal Complexation of Optically Pure Annulated Cyclopentadienes. Face Selectivity, Three-Dimensional Structural Features, and Utilization for Asymmetric Hydrogenation' see the whole document ---	1-11
P,X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.116, no.13, 29 June 1994, WASHINGTON, DC US pages 5985 - 5986 N. E. LEE ET AL 'Asymmetric Hydrogenation of Enamines With a Chiral Titanocene Catalyst' see the whole document ---	1-9
P,X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.115, no.26, 29 December 1993, WASHINGTON, DC US pages 12569 - 12570 R. D. BROENE ET AL 'Asymmetric Hydrogenation of Unfunctionalized Trisubstituted Olefins With a Chiral Titanocene Catalyst' see the whole document -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/US 94/07609

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US-A- 5227538	13-07-93
		US-A- 5292893	08-03-94
		US-A- 5220020	15-06-93
		CA-A- 2096747	22-05-92
		EP-A- 0558656	08-09-93
		JP-T- 6502867	31-03-94
